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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/767,421	01/22/2001	Michael J. Shamblott	JHU1750-1	9551

7590 01/28/2008

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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
01/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/767,421	SHAMBLOTT ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,9-13,15,22-32 and 34-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,9-13,15,22-32 and 34-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *January 22, 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 30, 2007 has been entered. Claims 1, 9-13, 15, 6, 22-32 and 34-38 are pending.

The term "EBD-derived cell" means an undifferentiated cell that composes an embryoid body.

The rejection of claims 1, 9-13, 15, 16, 22-32 and 34-38 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement made in the office action mailed September 24, 2007 is withdrawn in view of applicant's amendments.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 9-13, 15, 16, 22-32 and 34-38 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement as set forth in the office action mailed September 24, 2007. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable a use for EBD cells lacking detectable telomerase activity that is senescent cells. The uses disclosed in the specification each require the cells to actively divide. Senescent cells are not going to be useful for cell culture, tissue transplantation, tissue engineering, drug discovery or gene therapy. A senescent cell has quit dividing. Each disclosed use requires that the cells divide.

In support of this, attention is drawn the teachings of the specification, which states "we have isolated cells from human embryoid bodies (EB's), termed 'embryoid-body derived (EBD) cells', that are capable of long-term and robust proliferation in culture" specification, page 6, lines 14-16); "although EBD cells are not immortal, they display long-term growth and proliferation in culture" (specification, page 6, lines 22-23) and "although human EBD cells of the invention express telomerase activity, it may be desirable to enhance such expression to increase the lifespan of the cell (specification, page 21, lines 7-8). Thus, the EBD cells of the specification are taught to be quite different proliferative capacity from those claimed. It is the disclosed cells that are taught to be useful in differentiation methods to provide cells for transplantation therapies. The particular section of the specification that teaches EBD cells without detectable telomerase activity is set forth as determining the maximum number of divisions the cells can accomplish before senescing. There is no disclosure to use these cells in cell based therapies, nor in complete reading of the specification are these senescing cells taught to be part of the invention. When the specification as a whole is considered, on robust, proliferative EBD cells are invention.

The culture conditions for the EDB cells are all nonpermissive for the growth of hEGC's that is in the absence of LIF and the absence of a feeder layer (specification, page 65-66). Further, claims 11 and 30 state the EBD cells proliferate under suitable conditions that are nonpermissive for proliferation of hEGC's. The only culture conditions enabled by the specification that are nonpermissive for the proliferation of hEGC's are culture in media that lacks leukemia inhibitory factor and a fibroblast feeder layer. The claims should be so limited.

Thus at the time of the instant invention, the skilled artisan would have needed to engage in an undue amount of experimentation to make and use the invention as claimed.

Applicant argues the position of the office is incorrect because the claims do not state "senescent cells." Applicant argues that cells lacking detectable telomerase activity can be used for transplantation. Applicant cites Ostenfeld et al in support, stating Ostenfeld teaches human neural precursor cells express very low levels of telomerase activity at early passages and no detectable telomerase activity at later passages. Applicant argues the cells of Ostenfeld exhibited fiber outgrowth when implanted although there were no dividing cells in the graft. These arguments are not persuasive.

The physical characteristic of "lacking detectable telomerase activity" means the human EBD cells disclosed which, according to the specification, are undifferentiated, is at least undergoing senescence, and will lose their ability to differentiate for regeneration of tissues and organs for transplantation. (Specification, page 1, lines 10-14.) Further the specification states a lack of telomerase activity leads to cellular senescence (specification, page 77, lines 11-13). Thus, the claim does not need to state the cells are senescent since the phenotype "lacking detectable telomerase activity" leads to a senescent state.

In addition, senescent EBD cells or EBD cells lacking detectably telomerase are not contemplated for transplantation therapies. The specification states: EBD cells display robust and long-term proliferation in culture and have a use in transplantation therapies such as Parkinson's disease and ALS (specification, page 3, lines 2-5 and lines 11-15; and page 6, lines 14-16 and lines 22-25). The data presented in the specification demonstrates the lack of telomerase activity associated with limiting proliferation (specification, Example 8, page 77, lines 12-14). There is no contemplation of using these EBD cells in transplantation therapies. Given the description of EBD cells as having robust and long-term proliferation in culture, the argument could be that the cells in Example 8 are not EBD cells since they are not robust.

With regard to Ostenfeld, the relationship between the human neural precursors disclosed therein and the presently claimed EBD cells cannot be discerned. The Ostenfeld abstract provided by applicant does not state the source of the neural precursor cells. That is, are they EBD cells or further differentiated cells. It is noted Ostenfeld refers to the cells as "neural precursor cells" and the specification defines EBD cells expressing neural markers as neural lineage cells (Ostenfeld, line 1-2 and specification, page 11-14). Table 2 of the specification shows the detection of neural lineage markers, but it is not clear if these markers are the same markers exhibited by Ostenfeld. Without such data, it is not possible to discern if Ostenfeld and applicant had the same cells. As differentiation is a progression from undifferentiated to differentiated, the formation of neural precursor cells as taught by Ostenfeld may require particular growth/differentiation factors. If this is the case, then implanting the EBD cells of the claims would probably not differentiate into neural precursor cells of Ostenfeld or functioning neurons because of the lack of growth/differentiation factors. The implantation therefore in Ostenfeld of cells that lack detectable telomerase activity may be because 1) the precursor cells of Ostenfeld are sufficiently differentiation to develop in vivo into neuronal and 2) differentiation requires the cells quit dividing. Thus Ostenfeld may have implanted the neural precursor cells because they were known to develop in vivo into neurons, but the artisan would not have implanted EBD cells lacking detectable telomerase activity because they had already senesced.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 9-13, 15, 16, 22-32 and 34-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to EBD cells, which lack detectable telomerase activity. This is confusing because the specification teaches the EBD cells as having extensive proliferative capacity, clearly an indicator of telomerase activity (page 64, lines 16-18.) From the disclosure as a whole, the invention does not seem to be EBD cells lacking telomerase activity cells, but cells that are embryonic and proliferative.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9-13, 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,453,357 issued September 26, 1995 (Hogan) in view of Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731 (ref. AE).

Hogan teaches mouse embryoid body cells isolated from mouse embryoid bodies (EB's), rounded colonies of densely packed ES-like cells, produced by the culture of mouse primordial germ cells (col. 6, lines 19-49). Hogan describes the picking of single clones of EB-derived mouse cells, indicating clonal selection from a single EB-derived cell (col. 8, lines 5-9). Hogan offers motivation in stating ES cells from other mammals, such as humans, can be produced using the methods described therein for mouse (col. 5, lines 3-5 and col. 9, lines 18-11). Hogan offers additional motivation in stating derivatives of human ES cells, produced by the method disclosed therein, could treat neurodegenerative disease (col. 5, lines 32-34). Hogan also teaches the mouse EBD-cells to undergo at least 20 population doublings (col. 8, lines 14-16). Hogan further teaches that LIF make not be required for the maintenance of ES cells, which are interpreted to be the cells of the claims (col. 4, lines 55-

67).

Shamblott teaches embryoid bodies (EB's) produced from human primordial germ cells (hPGC's) (13729, col. 1, parag. 1-12). Shamblott offers motivation in stating the human pluripotent stem cells produced therein would provide for studies of human embryogenesis, transplantation therapies, and defining culture conditions and differential gene expression for cell-type differentiation (page 13730, col. 1, parag. 2, lines 1-8).

As the presently claimed cells are derived from human primordial germ cells, the ordinary artisan at the time of filing would have reasonably expected the physiological characteristics to be the same for the claimed cells and those of Hogan even given species differences. Thus, the cells of Hogan in view of Shamblott undergo at least 30 or at least 60 population doublings, proliferate under conditions nonpermissive for the proliferation of human EG cells, proliferate under culture conditions lacking LIF, a fibroblast feeder layer, or both, and transfectable with a retrovirus, lentivirus or both. There is no evidence to the contrary on the record. Products obvious over those in the art would be expected to have the same properties absent evidence to the contrary.

Therefore at the time of the present invention, it would have been obvious to produce human EBD-cells in view of the production of mouse EBD-cells as taught by Hogan in view of Shamblott teachings human EB's. The prior art offers the requisite teachings, suggestions and motivation to combine, and a reasonable expectation of success.

Claims 22-24, 27 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,453,357 issued September 26, 1995 (Hogan) in view of Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731 (ref. AE).

Hogan teaches a method of producing EBD-cells comprising culturing primordial germ cells to form an embryoid body), rounded colonies of densely packed ES-like cells, digesting the embryoid body with trypsin to provide EBD-cells and culturing the EBD-cells in

media comprising h bfgf2 (col. 6, lines 20-48). Hogan describes the picking of single clones of EB-derived mouse cells, indicating clonal selection from a single EB-derived cell (col. 8, lines 5-9). Hogan also teaches the mouse EBD-cells to undergo at least 20 population doublings, which encompasses 30 population doublings (col. 8, lines 14-16). Hogan further teaches that LIF make not be required for the maintenance of ES cells, which are interpreted to be the cells of the claims (col. 4, lines 55-67). LIF is required for the growth of EG cells as stated in the specification (specification, page 8m lines 2-3). Hogan teaches culture of EBD-cells on feeder cells, which is a matrix. Hogan offers motivation in stating ES cells from other mammals, such as humans, can be produced using the methods described therein for mouse (col. 5, lines 3-5 and col. 9, lines 18-11). Hogan offers additional motivation in stating derivatives of human ES cells, produced by the method disclosed therein, could treat neurodegenerative disease (col. 5, lines 32-34).

Shamblott teaches embryoid bodies (EB's) produced from human primordial germ cells (hPGC's) (13729, col. 1, parag. 1-12). Shamblott offers motivation in stating the human pluripotent stem cells produced therein would provide for studies of human embryogenesis, transplantation therapies, and defining culture conditions and differential gene expression for cell-type differentiation (page 13730, col. 1, parag. 2, lines 1-8).

Thus, at the time of filing, it would have been obvious to the ordinary artisan to follow the method of Hogan to produce human EBD cells given the method of producing human EB's from hPGC culture as taught by Shamblott given the teachings and motivations provided. The cited prior art provides the requisite teaching, suggestion and motivation, as well as a reasonable expectation of success.

Claims 22 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,453,357 issued September 26, 1995 (Hogan) in view of Shamblott et al (1998) Proced. Natl. Acad. Sci. 95, pp. 13726-13731 (ref. AE) further in view of Rohwedel

et al (1996) Cell Biol. Internat. 20, pp. 579-587 (ref. AC).

Hogan teaches a method of producing EBD-cells comprising culturing primordial germ cells to form an embryoid body), rounded colonies of densely packed ES-like cells, digesting the embryoid body with trypsin to provide EBD-cells and culturing the EBD-cells in media comprising h bfgf2 (col. 6, lines 20-48). Hogan offers motivation in stating ES cells from other mammals, such as humans, can be produced using the methods described therein for mouse (col. 5, lines 3-5 and col. 9, lines 18-11). Hogan offers additional motivation in stating derivatives of human ES cells, produced by the method disclosed therein, could treat neurodegenerative disease (col. 5, lines 32-34).

Shamblott teaches embryoid bodies (EB's) produced from human primordial germ cells (hPGC's) (13729, col. 1, parag. 1-12). Shamblott offers motivation in stating the human pluripotent stem cells produced therein would provide for studies of human embryogenesis, transplantation therapies, and defining culture conditions and differential gene expression for cell-type differentiation (page 13730, col. 1, parag. 2, lines 1-8).

Rohwedel teaches the culture of mouse EB cells on tissue culture plates coated with gelatin for morphological studies (page 580, col. 2, parag. 1, lines 14-18). Morphological studies are a part of a study of embryogenesis. It is noted that gelatin is a hydroxylation product of collagen I.

Thus, at the time of filing, it would have been obvious to the ordinary artisan to follow the method of Hogan to produce human EBD cells given the method of producing human EB's from hPGC culture as taught by Shamblott, culturing the EBD cells on collagen I coated plates given the teachings and motivations provided. The cited prior art provides the requisite teaching, suggestion and motivation, as well as a reasonable expectation of success.

Claims 25 and 26 are free of the prior art. At the time of filing the prior art did not teach or suggest methods of obtaining a human EBD cell comprising culturing resulting EBD cells in the particular media claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Fri, 6:00 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

January 17, 2008